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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/926,630	02/26/2002	Claudia Ulbrich	P67344US0	1109

136 7590 08/26/2004

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EXAMINER	
CANELLA, KAREN A	
ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 08/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/926,630	ULBRICH ET AL.	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 4 and 7-11 have been amended. Claims 1-16 are pending and examined on the merits.

Claim Objections

2. Claims 5 and 7 are objected to because of the following informalities:

Claim 5 recites "tumor cell a suspension of tumor cells" versus "tumor cell suspension".

Claim 7 is lacking the phrase "is induced" before the phrase "by cytokines".

Claim 9 recites the phrase "isolating the optionally evaluating" versus "isolating and optionally evaluating".

Appropriate correction is required.

Claim Rejections - 35 USC § 101

3. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

4. Claims 15 and 16 are rejected under 35 U.S.C. 101 because they are not presented in the format of a proper process claim. See MPEP 2173.05(q).

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(A) Claims 15 and 16 are drawn to the "use of a composition" are vague and indefinite. The claims are drawn to a method of using an agent, but fail to set forth any active, positive steps that define the claimed method.

(B) Claims, 1, 9 and 10 recite "transferred into a purified cell suspension". It is unclear if the comminuted tumor material is to be made into a suspension, or if said tumor material is to be added into (transferred to) a purified cell suspension. Claim 1 recites "a calculated amount of the above frozen tumor cell lysate is thawed". It is unclear how a portion of a frozen lysate can be thawed in the presence of the remainder of the lysate. It is also unclear into what the thawed lysate and cytokines is being added. For purpose of examination, the first clause of the claim will be read as "A composition obtainable by a process in which tumor material is evaluated, comminuted and made into a purified tumor cell suspension, which is then incubated with interferon-gamma and tocopherol acetate and frozen to form a tumor cell lysate" and the third clause of the claim will be read as "whereupon the tumor cell lysate is thawed, and a portion of the thawed lysate is added to said non-adherent dendritic cells with cytokines followed by incubation of the mixture, and harvesting of the mature dendritic cells". Claims 9 and 10 will be read as "made into a purified cell suspension".

(C) Claims 2 and 10 recite "autologous tumor material". It is unclear how the adjective "autologous" modifies the metes and bounds of "tumor material" and further defines claims 1 and 5 because neither claim 1 nor 5 references a patient to which the tumor material would be autologous.

(D) Claim 5 is vague and indefinite because it lacks a nexus between the harvesting of the mature dendritic cells and the preparation of the medicament as recited in the method objective.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

8. Claims 5-10, 13-16 are rejected under 35 U.S.C. 102(e) as being anticipated by Albert et al (US 2002/0146396, priority to 09/251,896, filed Feb 19, 1999).

Claim 5 is drawn to a method for preparing a medicament comprising the steps of preparing a tumor cell suspension and killing said tumor cells; isolating monocytes from blood and differentiating said monocytes into immature dendritic cells; incubating said immature dendritic cells with the killed tumor cell lysate to induce maturation of the dendritic cells; and harvesting of the mature dendritic cells. Claim 6 embodies the method of claim 5 wherein the monocytes are isolated from buffy coats, whole blood, leukapheresis or separated stem cells. Claim 7 embodies the method of claim 5 wherein the differentiation of monocytes into immature dendritic cells is induced by cytokines, Il-4 and GM-CSF with or without IFN-gamma. Claim 8 embodies the method of claim 5 wherein the maturing of the dendritic cells is included by PGE2 and TNF-alpha and/or Il-1B and Il-6 in addition to IL-4 and GM-CSF. Claims 9 and 10 embody the method of claim 5 wherein the tumor cell suspension and autologous tumor cell suspension is prepared by isolating and optionally evaluating tumor material, which is then comminuted and made into a purified cell suspension. Claim 13 embodies the method of claim 5 wherein the tumor cell lysates are killed by freezing. Claim 14 embodies the method of claim 5 wherein the mature dendritic cells are harvested when typical morphological characteristics are present and/or by characterization of surface antigens using fluorescent antibodies. Claims 15 and 16 are included with this rejection because it is unclear what is being claimed for the reasons set forth in the rejection under 112, 2nd and 101 above.

Albert et al disclose a method for maturing immature dendritic cells to mature dendritic cells comprising isolating monocytes from the peripheral blood and the culturing of said monocytes in the presence of monocyte conditioned medium or other factors including PGE2, TNF-alpha, IL-1B, IFN-gamma and necrotic cells (paragraphs [0083], [0086] and [0213]) to

induce immature dendritic cells. Albert et al disclose that exposure of the immature dendritic cells to necrotic cells, but not apoptotic cells induced expression of markers consistent with mature dendritic cells (paragraphs [0215, lines 9-13] and [0216, lines 5-6]) and that levels of cell surface CD40 doubled following exposure to necrotic cells (paragraph [0215], lines 13-15).. Albert et al discloses the receptor profile of immature dendritic cells and mature dendritic cells on page 18 and disclose that mature dendritic cells differ from immature dendritic cells in that the mature cells express the CD83 antigen both intercellularly and extracellularly as evidenced by the FACS assay presented in Figure 18 (paragraph [0187]), thus fulfilling the specific embodiments of claim 14 specifying characterization of surface antigens using fluorescent antibodies. Albert et al disclose that necrotic tumor cells were induced by repeated freezing and thawing (paragraph [0209], lines 6-7), thus fulfilling the specific embodiments of claim 5 drawn to preparing a tumor cell suspension and claim 13 specifying that the tumor cells are killed by freezing.

9. Claims 5-10 and 14-16 are rejected under 35 U.S.C. 102(b) as being anticipated by Holtl et al (Journal of Urology, March 1999, Vol. 161, pp. 777-782).

The specific embodiments of the claims are set forth above.

Holtl et al disclose a method for making a vaccine comprising culturing culturing human dendritic cells from buffy coats in the presence of Il-4 and GM-CSF (page 778, under the heading "Culture of dendritic cells"). Hotlt et al disclose the preparation of autologous tumor cell suspensions made from nephrectomy specimens which were minced, digested with collagenase and deoxyribonuclease, washed and plated in 96-well plates in order to eliminate non-adherent cells (page 779, under the heading "Preparation of tumor cell lysates"). Hotlt et al disclose that the autologous tumor cell lysate was added to the cultured dendritic cells with TNF-alpha and PGE2 (page 779, under the heading of "Pulsing of dendritic cells"), thus fulfilling the specific embodiment of claim 8. Hotlt et al disclose that the recovery of fully mature CD83+ dendritic cells after the antigen pulse ranged from 1-27% of the total peripheral blood mononuclear cells (page 780, first column, lines 8-11 and Page 778, figure 1), thus fulfilling the specific embodiment of claim 14 specifying characterization of surface antigens using fluorescent antibodies.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 5-11 and 14-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Holtl et al (Journal of Urology, March 1999, Vol. 161, pp. 777-782) in view of Schlom (In: Molecular Foundations of Oncology, 1991, S Broder, Ed, pp. 95-134).

Claim 11 embodies the method of claim 5 wherein the expression of membrane borne protein complexes is induced in the tumor cell suspension prior to the killing of the cells.

Holtl et al teach a method of making a therapeutic composition by the method comprising culturing human dendritic cells from buffy coats with the cytokines Il-4 and GM-CSF (page 778, under the heading "Culture of dendritic cells"); preparation of a tumor cell lysate from autologous tumor cells which have been minced, digested with collagenase and deoxyribonuclease, washed and plated in 96-well plates in order to eliminate non-adherent cells and lysed under hypotonic conditions (page 779, under the heading "Preparation of tumor cell lysates"). Holtlt et al teach that the autologous tumor cell lysate was added to the cultured dendritic cells with TNF-alpha and PGE2 (page 779, under the heading of "Pulsing of dendritic

cells"). Hotlt et al do not teach the induction of expression of membrane borne protein complexes prior to the killing of the tumor cells.

Schlom teaches that interferon's, such as IFN-gamma can up regulate the expression of several tumor associated antigens, such as melanoma antigens and carcinoma antigens and that this has been demonstrated using fresh biopsy specimens (bridging paragraph, page 109, second column to page 110, first column).

It would have been prima facie obvious at the time the claimed invention was made to incubate the tumor cell suspension with interferon gamma prior to the hypotonic lysis of the tumor cells. One of skill in the art would have been motivated to do so by the teachings of Schlom on the upregulation of tumor associated antigens in fresh biopsy samples by exposure to the interferons, specifically interferon gamma. One of skill in the art would have been motivated to exposure the tumor cell suspension to interferon gamma in order to increase the level of tumor associated antigen on the surface of said tumor cell in order to provide a greater level of tumor associated antigens within the thawed lysate.

13. Claims 1-11 and 13-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Albert et al (US 2002/0146396, priority to 09/251,896, filed Feb 19, 1999) in view of Schlom (In: Molecular Foundations of Oncology, 1991, S Broder, Ed, pp. 95-134).

The specific embodiments of claims 5-11 and 13-16 are set forth above. Claim 1 is drawn to a composition obtainable by a process in which tumor material is evaluated comminuted and suspended as a purified cell suspension, which said cell suspension if then incubated with IFN-gamma and tocopherol acetate and frozen to form a tumor cell lysate and in which monocytes are isolated from buff coats or whole blood and subsequently induced to differentiation into dendritic cells by incubation with cytokines and converted to non-adherent stage, whereupon a portion of the thawed lysate and cytokines are added to the non-adherent dendritic cells, the mixture is incubated and mature dendritic cells are harvested. Claim 2 embodies the composition of claim 1 wherein autologous tumor material has been used for the preparation. Claim 3 embodies the method of claim 1 wherein Il-4 and GM-CSF are added for differentiation into immature dendritic cells. Claim 4 is drawn to a medicament comprising the composition of claim 1.

Albert et al teach a method for maturing immature dendritic cells to mature dendritic cells comprising isolating monocytes from the peripheral blood and the culturing of said monocytes in the presence of monocyte conditioned medium or other factors including PGE2, TNF-alpha, IL-1B, IFN-gamma and necrotic cells (paragraphs [0083], [0086] and [0213]) to induce immature dendritic cells. Albert et al teach that exposure of the immature dendritic cells to necrotic cells, but not apoptotic cells induced expression of markers consistent with mature dendritic cells (paragraphs [0215, lines 9-13] and [0216, lines 5-6]) and that levels of cell surface CD40 doubled following exposure to necrotic cells (paragraph [0215], lines 13-15).. Albert et al teach the receptor profile of immature dendritic cells and mature dendritic cells on page 18 and disclose that mature dendritic cells differ from immature dendritic cells in that the mature cells express the CD83 antigen both intercellularly and extracellularly as evidenced by the FACS assay presented in Figure 18 (paragraph [0187]), thus fulfilling the specific embodiments of claim 14 specifying characterization of surface antigens using fluorescent antibodies. Albert et al teach that necrotic tumor cells were induced by repeated freezing and thawing (paragraph [0209], lines 6-7), thus fulfilling the specific embodiments of claim 5 drawn to preparing a tumor cell suspension and claim 13 specifying that the tumor cells are killed by freezing. Albert et al do not teach the induction of membrane-borne protein complexes prior to the killing of the tumor cells

Schlom teaches that interferons, such as IFN-gamma can up regulate the expression of several tumor associated antigens, such as melanoma antigens and carcinoma antigens and that this has been demonstrated using fresh biopsy specimens (bridging paragraph, page 109, second column to page 110, first column).

It would have been prima facie obvious at the time the claimed invention was made to incubate the tumor cell suspension with interferon gamma prior to the killing of the tumor cells. One of skill in the art would have been motivated to do so by the teachings of Schlom on the upregulation of tumor associated antigens in fresh biopsy samples by exposure to the interferons, specifically interferon gamma. One of skill in the art would have been motivated to exposure the tumor cell suspension to interferon gamma in order to increase the level of tumor associated antigen on the surface of said tumor cell in order to provide a greater level of tumor associated antigens within the thawed lysate.

14. Claims 1-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Albert et al (US 2002/0146396) and Schlom (In: Molecular Foundations of Oncology, 1991, S Broder, Ed, pp. 95-134) as applied to claims 1-11 and 13-16 above, and further in view of Baust et al (U.S. 6,045,990).

The specific embodiments of claims 5-11 and 13-16 are set forth above. Claim 12 embodies the method of claim 11 wherein the expression of the membrane-borne protein complexes is induced by interferon-gamma and tocopherol acetate.

The teachings of Albert et al and Schlom which render obvious claims 5-11 and 13-16 are set forth above. Neither Albert et al nor Schlom teach the incubation of the tumor cell suspension with tocopherol acetate.

Baust et al teach that freezing media comprising vitamin E (tocopherol acetate) preserve plasma membrane integrity (column 6, lines 49-53). Baust et al corroborate what is well known in the art, that tocopherol acetate is an anti-oxidant (column 13, lines 33-36). Baust et at corroborate the teachings of Albert et al in the observation that necrotic cell death is the dominant mechanism of cell death in frozen cells (column 14, lines 5-14).

It would have been prima facie obvious at the time the claimed invention was made to incubate the tumor cell suspension with interferon gamma and tocopherol acetate before the cells are frozen to form a tumor cell lysate. One of skill in the art would have been motivated to do so in order to protect the tumor associated antigens on the surface of the tumor cells from oxidative damage during the freezing and thawing of the tumor cell lysate. One of skill in the art would have been motivated to avoid oxidative damage to the tumor associated antigens in order to preserve the integrity of said antigens in the tumor cell lysate, in order that a higher level of tumor associated antigen can be presented for uptake into the immature dendritic cells.

Conclusion

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10 a.m. to 9 p.m. M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571)272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.
8/23/2004

Karen A. Canella

KAREN A. CANELLA PH.D
PRIMARY EXAMINER